

**WHAT IS CLAIMED IS:**

1. A composition comprising:  
demineralized bone matrix (DBM); and  
a collagen protein;  
5 wherein the composition is cross-linked.
2. The composition of Claim 1, wherein the composition is chemically crosslinked with a carbodiimide crosslinking agent.
3. The composition of Claim 2, wherein the carbodiimide crosslinking agent is N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDC).
- 10 4. The composition of Claim 2, wherein the composition is chemically cross-linked in the presence of N-hydroxysuccinimide (NHS).
5. The composition of Claim 1, further comprising one or more growth factors.
6. The composition of Claim 1, wherein the composition comprises from 2  
15 to 95 wt/% DBM.
7. The composition of Claim 1, wherein the composition comprises from 55 to 85 wt/% DBM.
8. The composition of Claim 1, wherein the DBM comprises particles of the DBM dispersed in the collagen.
- 20 9. The composition of Claim 1, wherein the collagen protein is in a porous scaffolding.
10. The composition of Claim 9, wherein the DBM comprises particles of DBM dispersed in the porous scaffolding.

11. The composition of Claim 8, wherein the DBM particles have an average particle size of up to 5 mm.
12. The composition of Claim 8, wherein the DBM particles have an average particle size ranging from 53 to 850  $\mu\text{m}$ .
- 5           13. The composition of Claim 1, wherein the composition is chemically crosslinked with a compound selected from the group consisting of gluteraldehyde, formaldehyde, 1,4-butanediol diglycidyl ether, hydroxypyridinium, hydroxylysylpyridinium, and formalin.
- 10           14. The composition of Claim 1, wherein the composition is crosslinked by irradiation.
15. The composition of Claim 1, wherein the composition is crosslinked by photooxidation.
16. The composition of Claim 1, wherein the composition is crosslinked via an enzymatic process.
- 15           17. The composition of Claim 16, wherein the collagen protein is crosslinked via the action of tissue transglutaminase.
18. The composition of Claim 16, wherein the composition is crosslinked with lysyl oxidase.
19. The composition of Claim 1, wherein the composition is crosslinked by
- 20           a dehydrothermal treatment.
20. The composition of Claim 1, wherein the composition is crosslinked under acidic conditions.
21. The composition of Claim 1, wherein the collagen protein is

crosslinked using e-beam irradiation, gamma irradiation, or light.

22. The composition of Claim 21, wherein the collagen protein is crosslinked using pulsed light.

23. The composition of Claim 1, further comprising a spacer.

5        24. The composition of Claim 23, wherein the spacer is a polyoxyalkyleneamine spacer or a polyethylene glycol spacer.

25. The composition of Claim 1, wherein the composition further comprises vinyl pyrrolidinone or methyl methacrylate.

26. The composition of Claim 1, further comprising an additive selected  
10        from the group consisting of collagenase inhibitors, growth factors, antibodies, metalloproteinases, cell attachment fragment(s), and combinations thereof.

27. The composition of Claim 26, wherein the additive is bound to the collagen or DBM.

28. The composition of Claim 26, wherein the additive is not bound to the  
15        collagen or DBM.

29. The composition of Claim 1, wherein the composition is crosslinked by glycation or glycosylation.

30. The composition of Claim 1, wherein the crosslinks are pentosidine crosslinks.

20        31. The composition of Claim 1, wherein the crosslinks are epsilon(gamma-glutamyl)lysine crosslinks.

32. A method of making a composition comprising a collagen protein and demineralized bone matrix, the method comprising:

crosslinking the composition.

33. The method of Claim 32, wherein the composition is chemically crosslinked with a carbodiimide crosslinking agent.

5        34. The method of Claim 33, wherein the carbodiimide is N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDC).

35. The method of Claim 33, wherein the composition is chemically cross-linked in the presence of N-hydroxysuccinimide (NHS).

36. The method of Claim 35, wherein the NHS is present at an EDC/NHS ratio of 1:2 to 2:5.

10        37. The method of Claim 35, wherein the NHS is present at an EDC/NHS ratio of 1:2, 2:3 or 2:5.

38. The method of Claim 32, further comprising dispersing particles of the demineralized bone matrix in a collagen slurry, casting the slurry into the cavity of a mold and freeze drying the cast slurry to form a porous scaffolding comprising  
15        the collagen protein and particles of the demineralized bone matrix.

39. The method of Claim 38, wherein the slurry is an aqueous slurry.

40. The method of Claim 38, wherein crosslinking comprises:

infiltrating a carbodiimide crosslinking agent into pores of the porous scaffolding; and

20        allowing the carbodiimide cross-linking agent to react with the collagen protein and/or the DBM to form cross-links.

41. The composition of Claim 32, wherein the crosslinking results from culturing a non-crosslinked matrix *in vivo* to allow collagen crosslinking by

cellular mechanisms.

42. A method of treatment comprising implanting a composition comprising demineralized bone matrix (DBM) and a collagen protein into a mammal, wherein the composition is crosslinked.

5           43. The method of Claim 42, wherein the composition is chemically crosslinked with a carbodiimide crosslinking agent.

44. The method of Claim 42, wherein the composition is implanted into the spine of the mammal.

45. The method of Claim 42, wherein the composition is implanted into an  
10           intervertebral space of the mammal.

46. The method of Claim 42, wherein the composition is implanted into the site of a trauma injury.

47. The method of Claim 42, wherein the composition is implanted into a craniomaxillofacial cavity.

15           48. The method of Claim 42, wherein the mammal is a human.

49. A composition comprising:

demineralized bone matrix (DBM); and

a collagen protein;

wherein the composition is cross-linked via an amide linkage.

20           50. The composition of Claim 49, further comprising one or more growth factors.

51. The composition of Claim 49, wherein the composition comprises from 2 to 95 wt/% DBM.

52. The composition of Claim 49, wherein the composition comprises from 55 to 85 wt/% DBM.

53. The composition of Claim 49, wherein the composition comprises particles of the DBM dispersed in the collagen protein.

5 54. The composition of Claim 49, wherein the collagen protein is in a porous scaffolding.

55. The composition of Claim 54, wherein the composition comprises particles of the DBM dispersed in the porous scaffolding.

10 56. The composition of Claim 55, wherein the DBM particles have a particle size of up to 5 mm.

57. The composition of Claim 55, wherein the DBM particles have a particle size of from 53 to 850  $\mu\text{m}$ .